

Supplementary Information

Molecule Name	AG-690/12890456	AK-968/11841158	AP-064/41252894	AT-057/42811840	AG-690/11627255	AK-918/43446361	AF-399/32354064	AK-968/41926571	AK-968/12384193	AN-646/1521503	AP-064/41252984	procyanidin B2
Allergy	0.46	0.47	0.37	0.51	0.39	0.38	0.53	0.64	0.54	0.58	0.56	0.31
Alzheimer	0.38	0.61	0.49	0.52	0.54	0.48	0.18	0.25	0.49	0.56	0.58	0.29
Angina	0.57	0.26	0.53	0.44	0.42	0.4	0.4	0.39	0.5	0.44	0.47	0.26
Arthritis	0.68	0.57	0.7	0.54	0.63	0.55	0.68	0.48	0.59	0.71	0.59	0.65
Asthma	0.62	0.51	0.71	0.63	0.76	0.67	0.37	0.71	0.59	0.68	0.68	0.62
Bacterial	0.28	0.2	0.27	0.23	0.23	0.28	0.18	0.27	0.38	0.27	0.18	0.19
Cancer	0.64	0.74	0.69	0.65	0.77	0.69	0.43	0.31	0.76	0.54	0.71	0.64
Depression	0.63	0.78	0.62	0.62	0.61	0.58	0.44	0.53	0.45	0.53	0.7	0.13
Diabetes	0.32	0.45	0.37	0.58	0.39	0.42	0.25	0.34	0.44	0.44	0.46	0.32
HIV	0.73	0.71	0.83	0.7	0.84	0.74	0.39	0.7	0.79	0.74	0.81	0.4
Heart Failure	0.79	0.61	0.83	0.58	0.67	0.52	0.56	0.61	0.75	0.7	0.71	0.49
Hyperlipidemia	0.57	0.72	0.57	0.71	0.7	0.66	0.65	0.63	0.5	0.63	0.64	0.51
Hypertension	0.5	0.35	0.36	0.51	0.35	0.42	0.47	0.36	0.67	0.74	0.44	0.14
Inflammation	0.8	0.81	0.81	0.83	0.84	0.81	0.87	0.8	0.83	0.82	0.89	0.21
Migraine	0.75	0.76	0.77	0.75	0.76	0.76	0.34	0.51	0.72	0.69	0.78	0.5
Mycosis	0.24	0.55	0.39	0.31	0.48	0.5	0.61	0.5	0.45	0.48	0.49	0.4
Obesity	1	0.96	0.99	0.94	0.99	0.84	0.99	0.85	0.86	0.88	0.99	0.96
Osteoporosis	0.47	0.54	0.51	0.34	0.48	0.52	0.42	0.52	0.41	0.28	0.54	0.68
Pain	0.48	0.53	0.56	0.5	0.52	0.4	0.61	0.33	0.39	0.5	0.36	0.04
Parkinson	0.2	0.22	0.21	0.23	0.21	0.19	0.28	0.32	0.33	0.42	0.18	0.16
Psoriasis	0.3	0.34	0.31	0.32	0.34	0.31	0.21	0.42	0.35	0.46	0.53	0.45
Schizophrenia	0.27	0.34	0.35	0.29	0.3	0.31	0.12	0.31	0.51	0.22	0.23	0.84
Skin Diseases	0.5	0.43	0.47	0.54	0.46	0.47	0.67	0.37	0.55	0.56	0.54	0.72
Thrombosis	0.41	0.23	0.43	0.21	0.34	0.38	0.11	0.33	0.43	0.18	0.29	0.57
Viral	0.67	0.69	0.66	0.65	0.6	0.46	0.84	0.62	0.42	0.63	0.67	0.26

Figure S1. The therapeutic activity of the top 11 molecules along with a known NFkB inhibitor by MetaDrug/MetaCore™. In general, values greater than 0.50 indicate that the molecules are active as per the scores from the QSAR models. Only numerical values indicating activity scores over 0.50 were highlighted in the table for clarity and simplicity. The coloring scheme increases in intensity with greater therapeutic values. Pyocyanidin B2 was used as the control NFkB inhibitor.

Molecule Name	AG-690/12890456	AK-968/11841158	AP-064/41252894	AT-057/42811840	AG-690/11627255	AK-918/43446361	AF-399/32354064	AK-968/41926571	AK-968/12384193	AN-646/15215003	AP-064/41252984	B2
AMES	0.52	0.58								0.41	0.46	0.34
Anemia	0.31	0.16	0.16	0.24	0.25	0.5	0.39	0.33	0.16	0.3	0.25	0.2
Carcinogenicity	0.24	0.47	0.26	0.36	0.36	0.38	0.25	0.24	0.31	0.34	0.41	0.08
Carcinogenicity Mouse Female	0.26	0.38	0.25	0.34	0.33	0.47	0.27	0.45	0.3	0.42	0.4	0.12
Carcinogenicity Mouse Male	0.38	0.46	0.36	0.45	0.37	0.46	0.29	0.41	0.41	0.45	0.44	0.34
Carcinogenicity Rat Female	0.35	0.35	0.33	0.2	0.26	0.33	0.35	0.18	0.18	0.3	0.32	0.07
Carcinogenicity Rat Male	0.18	0.43	0.22	0.26	0.2	0.29	0.34	0.09	0.14	0.26	0.34	0.11
Cardiotoxicity	0.09	0.06	0.1	0.04	0.1	0.08	0.19	0.11	0.13	0.05	0.1	0.84
Cytotoxicity model, -log GI50 (M)	4.64	5.35	5.2	5.05	4.83	4.89	4.47	5.89	5.4	6.04	4.86	5.11
Epididymis toxicity	0.44	0.49	0.41	0.48	0.48	0.57	0.53	0.19	0.07	0.3	0.49	0.61
Genotoxicity	0.31	0.36	0.25	0.46	0.3	0.31	0.36	0.33	0.3	0.28	0.3	0.42
Hepatotoxicity	0.33	0.4	0.28	0.31	0.3	0.29	0.33	0.17	0.26	0.23	0.32	0.39
Kidney Necrosis	0.3	0.3	0.27	0.29	0.27	0.22	0.25	0.09	0.05	0.1	0.41	0.38
Kidney Weight Gain	0.09	0.1	0.08	0.15	0.1	0.21	0.11	0.06	0.06	0.14	0.13	0.06
Liver Cholestasis	0.32	0.26	0.32	0.46	0.32	0.37	0.55	0.43	0.1	0.35	0.34	0.65
Liver Lipid Accumulation	0.23	0.47	0.22	0.31	0.21	0.27	0.2	0.2	0.22	0.36	0.27	0.43
Liver Necrosis	0.39	0.39	0.41	0.36	0.31	0.3	0.4	0.17	0.56	0.24	0.12	0.98
Liver Weight Gain	0.09	0.26	0.12	0.13	0.09	0.14	0.14	0.12	0.32	0.21	0.09	0.89
MRTD*	0.33	0.19	0.04	0.44	0.5	0.58	0.13	0.06	0.06	0.14	-0.04	0.45
Nasal pathology	0.11	0.06	0.11	0.08	0.07	0.07	0.15	0.09	0.02	0.07	0.14	0.19
Nephron Injury	0.34	0.29	0.32	0.29	0.31	0.3	0.2	0.1	0.29	0.12	0.28	0.7
Nephrotoxicity	0.31	0.28	0.31	0.31	0.3	0.31	0.27	0.18	0.2	0.12	0.3	0.37
Neurotoxicity	0.48	0.49	0.45	0.4	0.36	0.48	0.56	0.3	0.17	0.18	0.47	0.23
Pulmonary toxicity	0.09	0.09	0.08	0.08	0.09	0.09	0.11	0.11	0.04	0.17	0.07	0.37
SkinSens, EC3	15.16	12.35	12.52	16.53	12.46	16.53	13.44	18.67	14.11	39.7	16.56	9.84
Testicular toxicity	0.22	0.41	0.24	0.25	0.26	0.33	0.37	0.34	0.21	0.51	0.33	0.39
Reactive**	R	OK	OK	R	OK	OK	OK	OK	R	OK	OK	

* Maximum Recommended Therapeutic Dose, log mg/kg-bm/day, range is from -5 to 3. Cutoff is 0.5. Chemicals with high log MRTDs can be classified as mildly toxic compounds, chemicals with low log MRTDs as highly toxic compounds.

** Metabolites contain reactive groups

Figure S2. The predicted toxicity effects of the top 11 molecules along with a known NF-κB inhibitor. The ligands were analysed using the MetaDrug/MetaCore™ platform. In general, values greater than 0.50 indicate that the molecules are toxic as per the scores from the QSAR models. Only numerical values indicating toxicity scores over 0.50 were highlighted in the table for clarity and simplicity. White boxes indicate no toxicity or nonsignificant toxicity with a score less than 0.50. The coloring scheme increases in intensity with greater toxicity values.

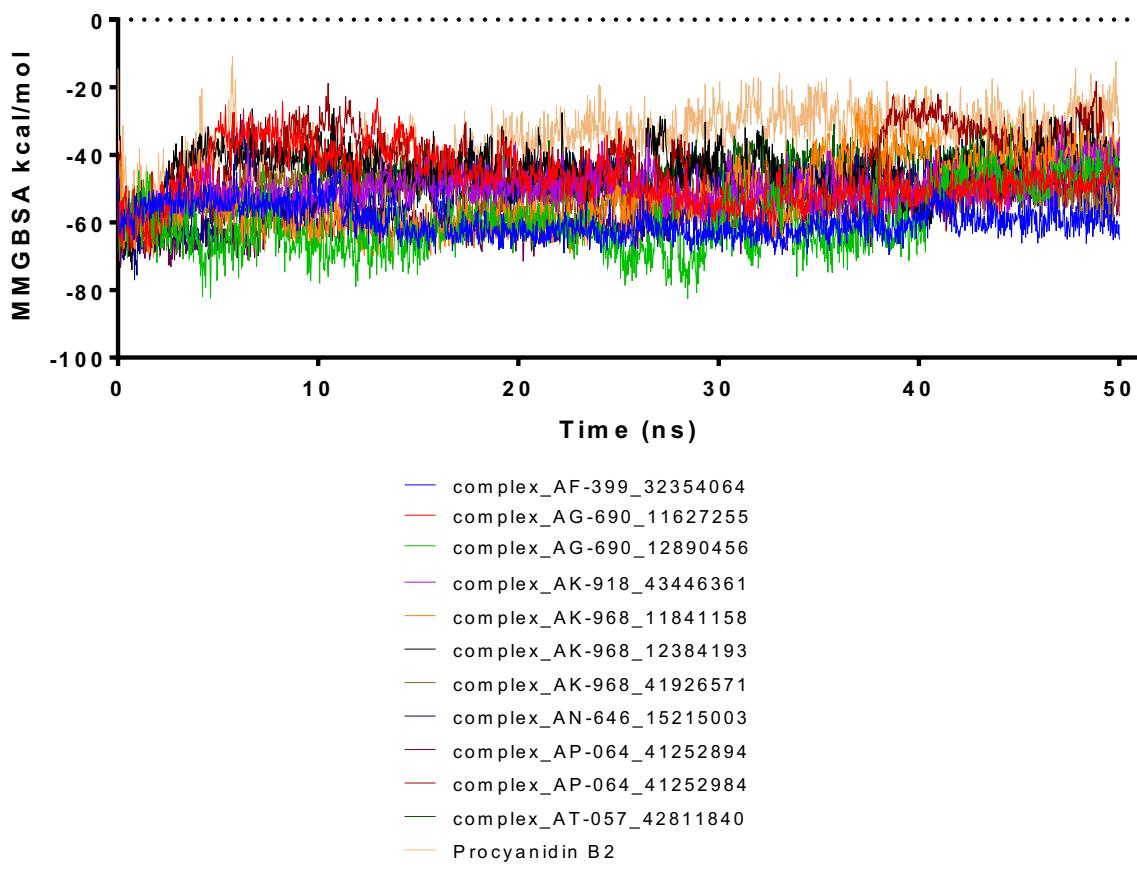


Figure S3. MM/GBSA free energy analysis for the top 11 hit ligands along with NFkB inhibitor (Procyanidin B2) at the binding pocket of NFkB/ I κ B α throughout the 50 ns MD simulations.

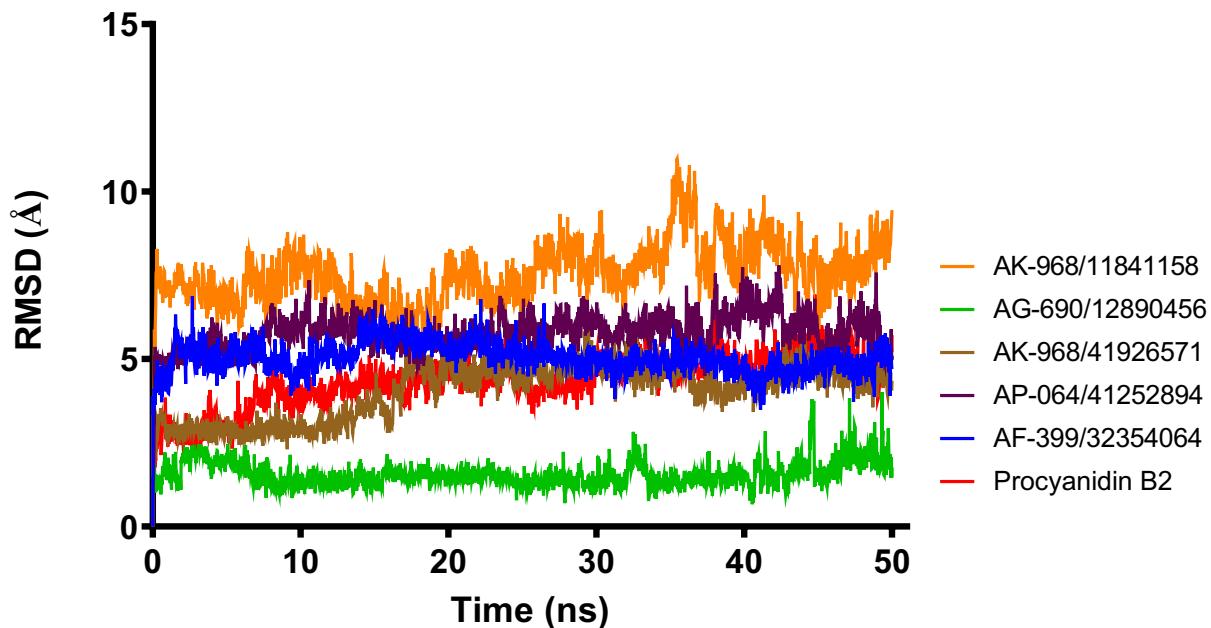


Figure S4. RMSD ligand fit protein graphs. Average RMSD values in Å were 1.57, 4.05, 5.03, 5.78, 7.55 and 4.37 for AG-690/12890456, AK-968/41926571, AF-399/32354064, AP-064/41252894, AK-968/11841158 and Pyocyanidin B2 used as the control NFkB inhibitor respectively.

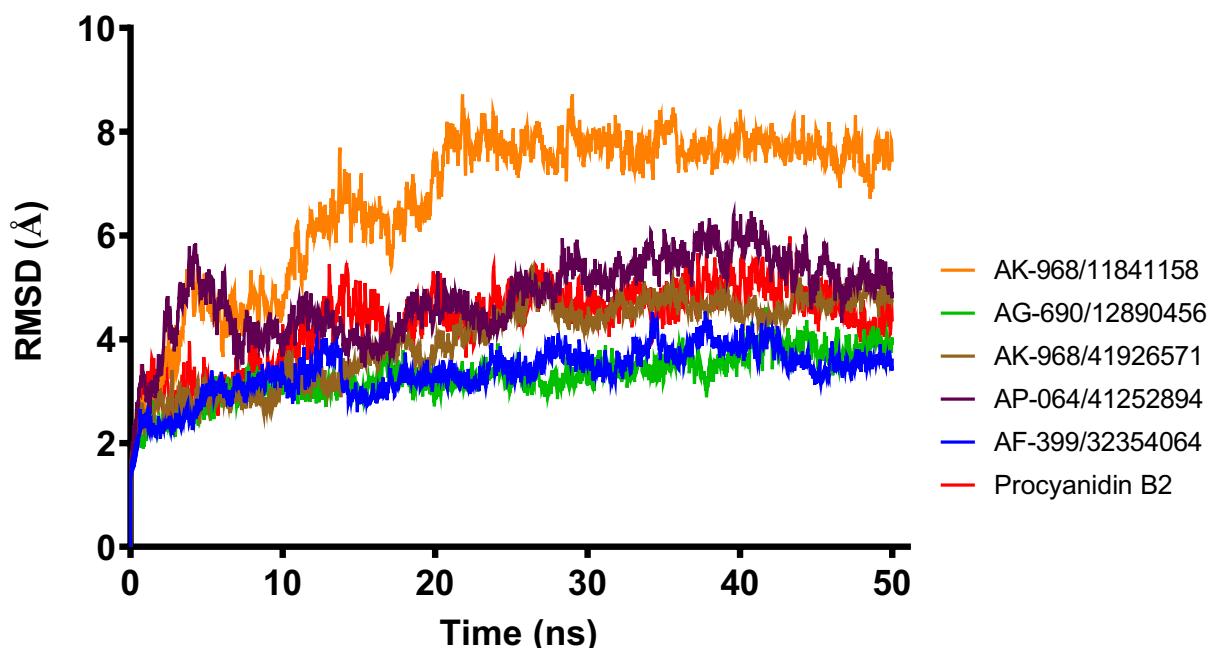


Figure S5. RMSD evolution of the carbon-alpha atoms over a 50 ns MD simulation with NFkB/ IκB α . The hit ligands from the SPECS library were selected after MM/GBSA free energy analysis and post-docking MetaCore analysis. Pyocyanidin B2 was used as the control NFkB inhibitor.

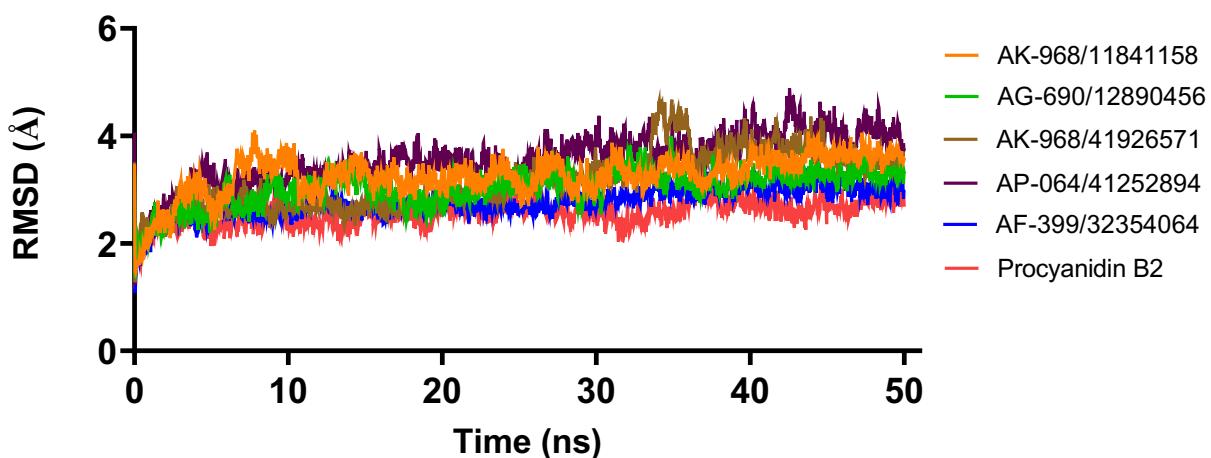
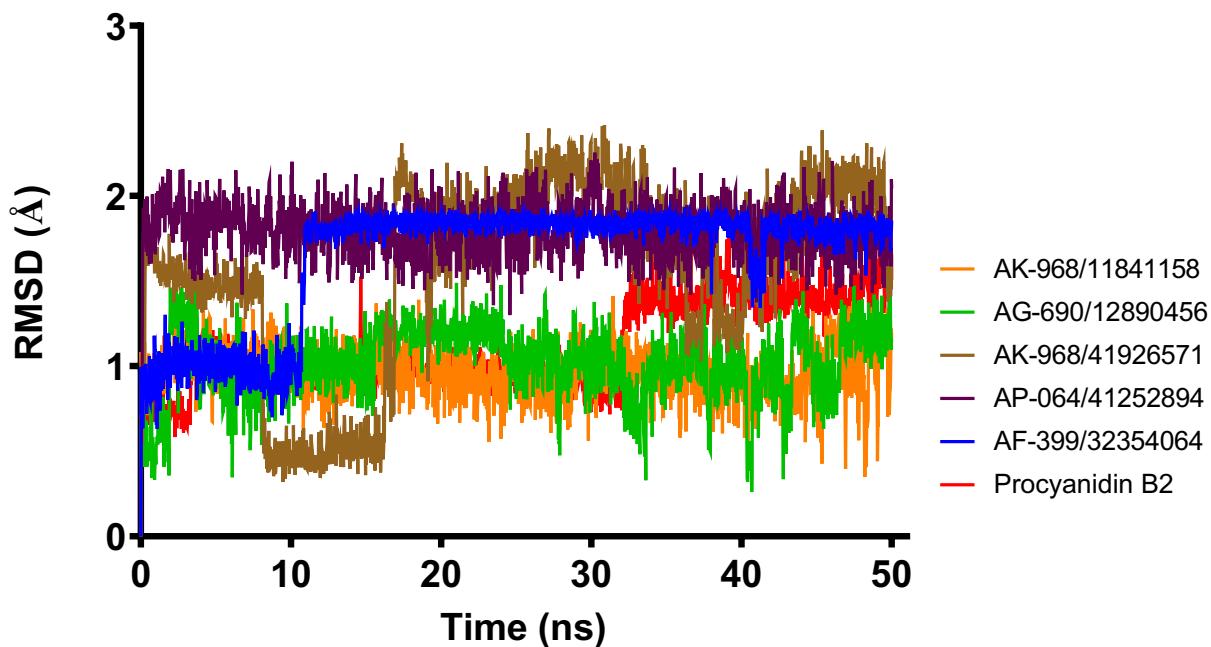


Figure S7. RMSD evolution over time for the backbone atoms covering the PEST sequence (residues 276-287) throughout the 50 ns MD simulation with the NF- κ B-I κ B α (p50/p65) complex. Procyanidin B2 is used the positive control.

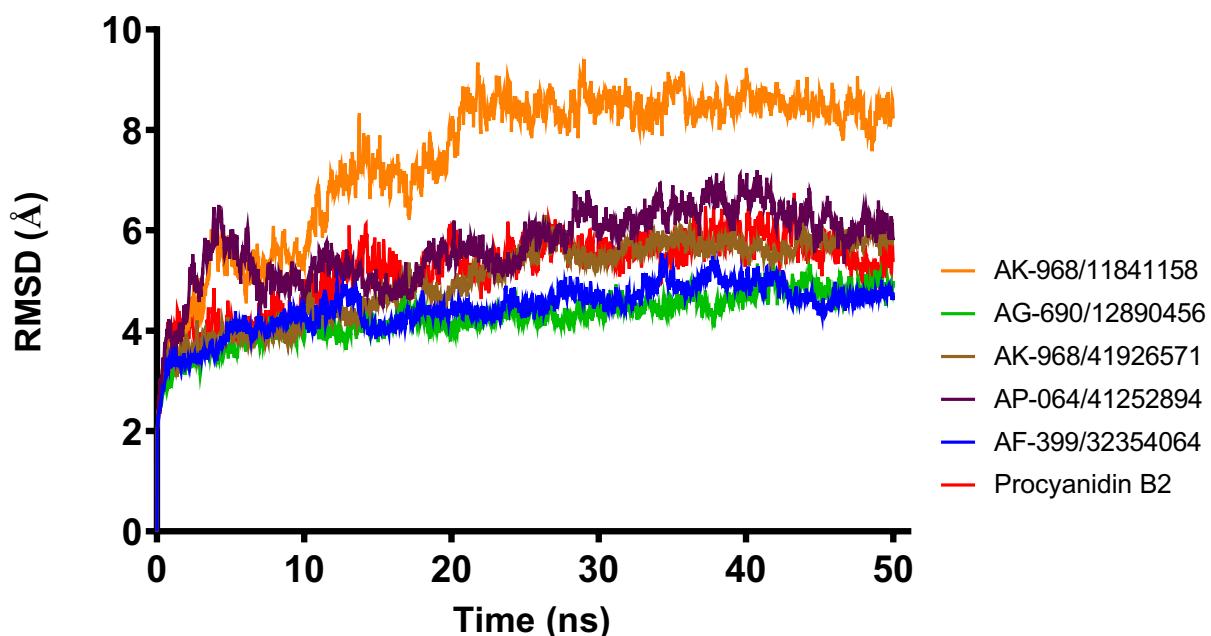


Figure S8. RMSD evolution of the side-chain atoms over a 50 ns MD simulation with with NFkB/ IkB α . The hit ligands from the SPECS library were selected after MM/GBSA free energy analysis and post-docking MetaCore analysis. Pyocyanidin B2 was used as the control NFkB inhibitor.

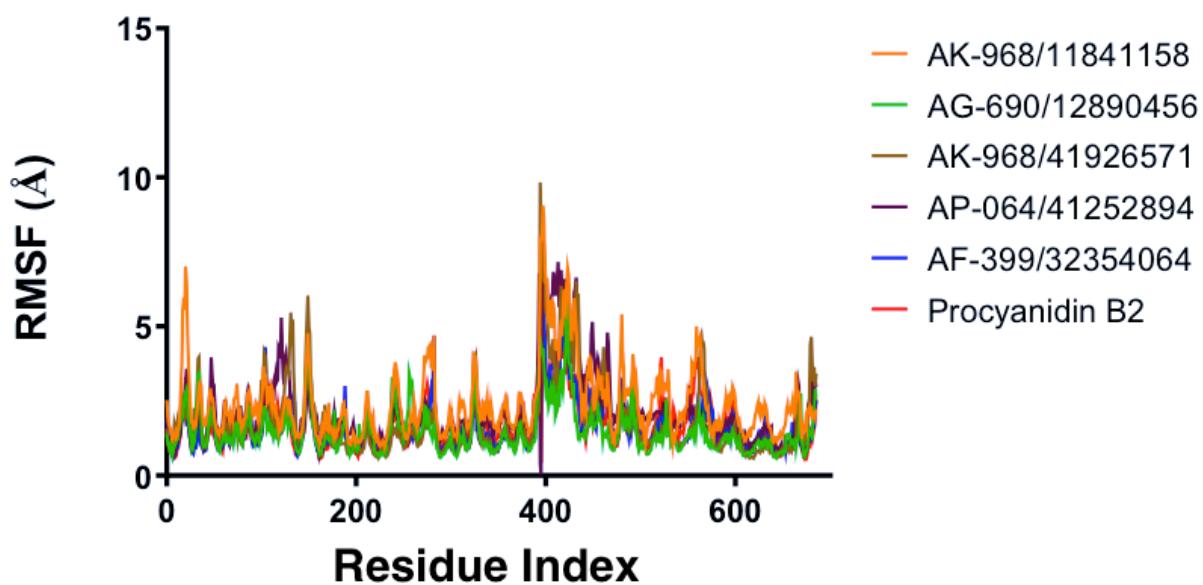


Figure S9. RMSF evolution over time for the carbon-alpha atoms during a 50 ns MD simulation with with NfkB/ IkB α . The hit ligands from the SPECS library were selected after MM/GBSA free energy analysis and post-docking MetaCore analysis. Pyocyanidin B2 was used as the control NFkB inhibitor.

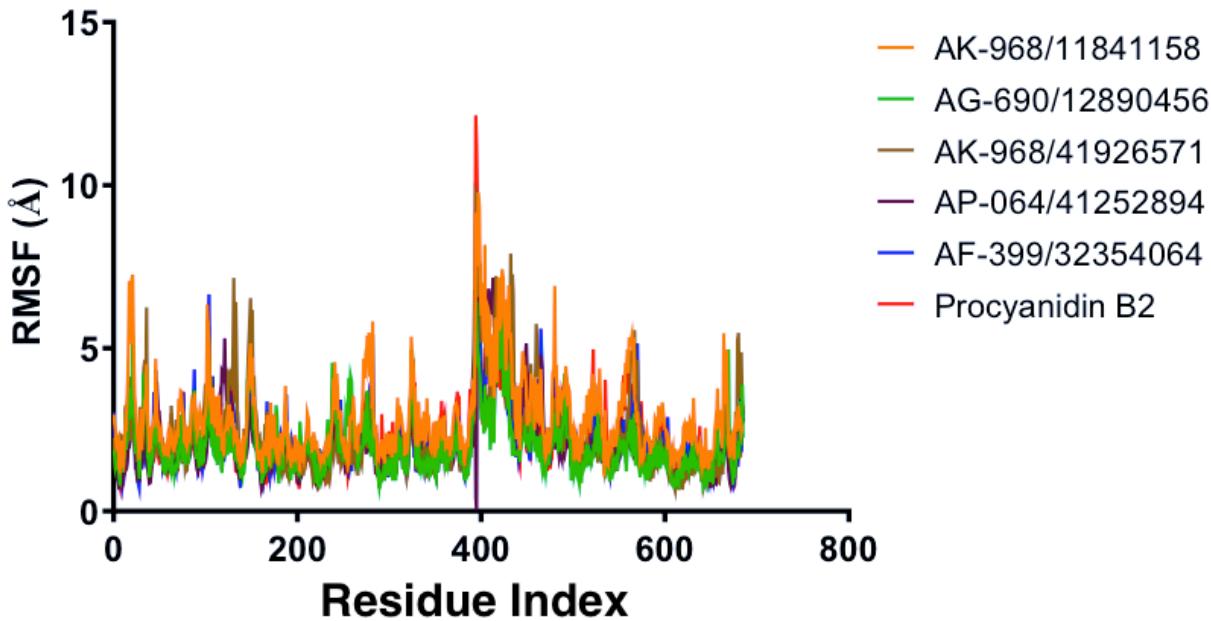


Figure S10. RMSF evolution over time for the side-chain atoms during a 50 ns MD simulation with NFkB/ IkBa. The hit ligands from the Specs library were selected after MM/GBSA free energy analysis and post-docking MetaCore analysis. Pyocyanin B2 was used as the control NFkB inhibitor.

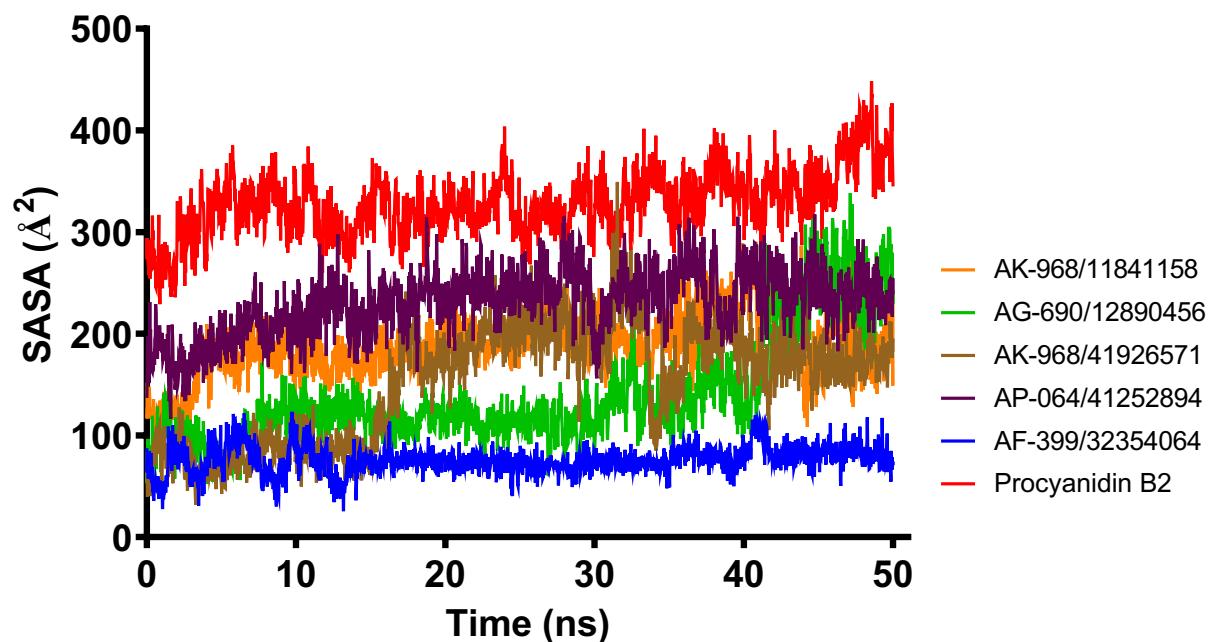


Figure S11. Solvent Accessible Surface Area (SASA) in \AA^2 of the hit ligands and a control inhibitor during 50 ns MD simulations with NFkB/ IkBa. The hit ligands from the SPECS library were selected after MM/GBSA free energy analysis and post-docking MetaCore analysis. Pyocyanin B2 was used as the control NFkB inhibitor.

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Formula	C20H21N3O3	C23H17FN2O	C22H19IN2O3	C17H17N3O2S	C21H18N2O2	C24H25N3O2	C16H14BrNO3	C19H16CIN3O2	C20H13Br2IN4O3	C16H15BrN6OS	C17H16ClIN2O2	C30H25O12
MW	351.406	356.4	486.309	327.4	330.387	387.483	348.196	353.81	644.061	419.3	442.68	577.519
RuleOf5	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
RBN	5	4	7	4	6	5	6	5	4	6	6	3
HBA	6	2	5	5	4	3	4	3	5	2	4	12
HBG	3	1	2	3	2	1	1	1	3	1	2	9
Prot-bind, log t	0.17	-0.07	0.11	-0.01	-0.03	-0.03	-0.07	0.29	0.11	-0.36	-0.08	-0.03
Prot-bind, %	90.23	87.23	83.67	87.73	90.53	79.86	85.86	77.36	85.99	79.39	88.18	84.55
G-LogP	2.74	3.07	2.53	2.44	2.95	2.21	3.07	2.98	2.16	3.79	2.84	3.36
WSol, log mg/L	0.55	0.89	0.38	1.8	1.26	1.6	2.32	1.06	1.26	1.63	1.63	0.68

Figure S12. The ADME properties of the top 11 molecules along with a known NFkB inhibitor. Pyocyanidin B2 was used as the control NFkB inhibitor.

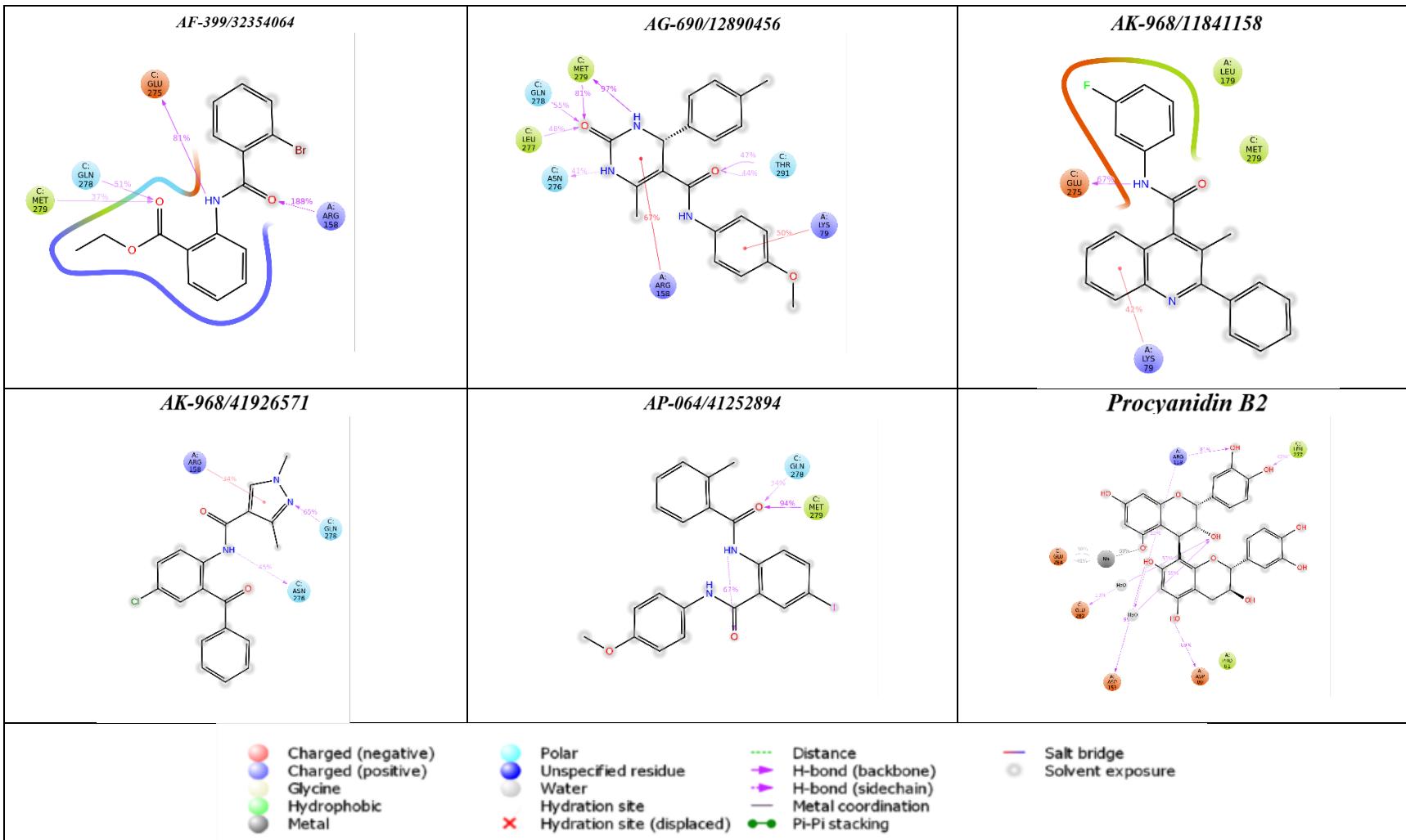


Figure S13. The ligand-protein interaction diagrams of the identified 5 ligands AF-399/32354064, AG-690/12890456, AK-968/11841158, AK-968/41926571 and AP-064/41252894 and the reference compound Procyanidin B2 in the active site of the NF-κB/IκB α complex throughout the 50 ns MD simulations.

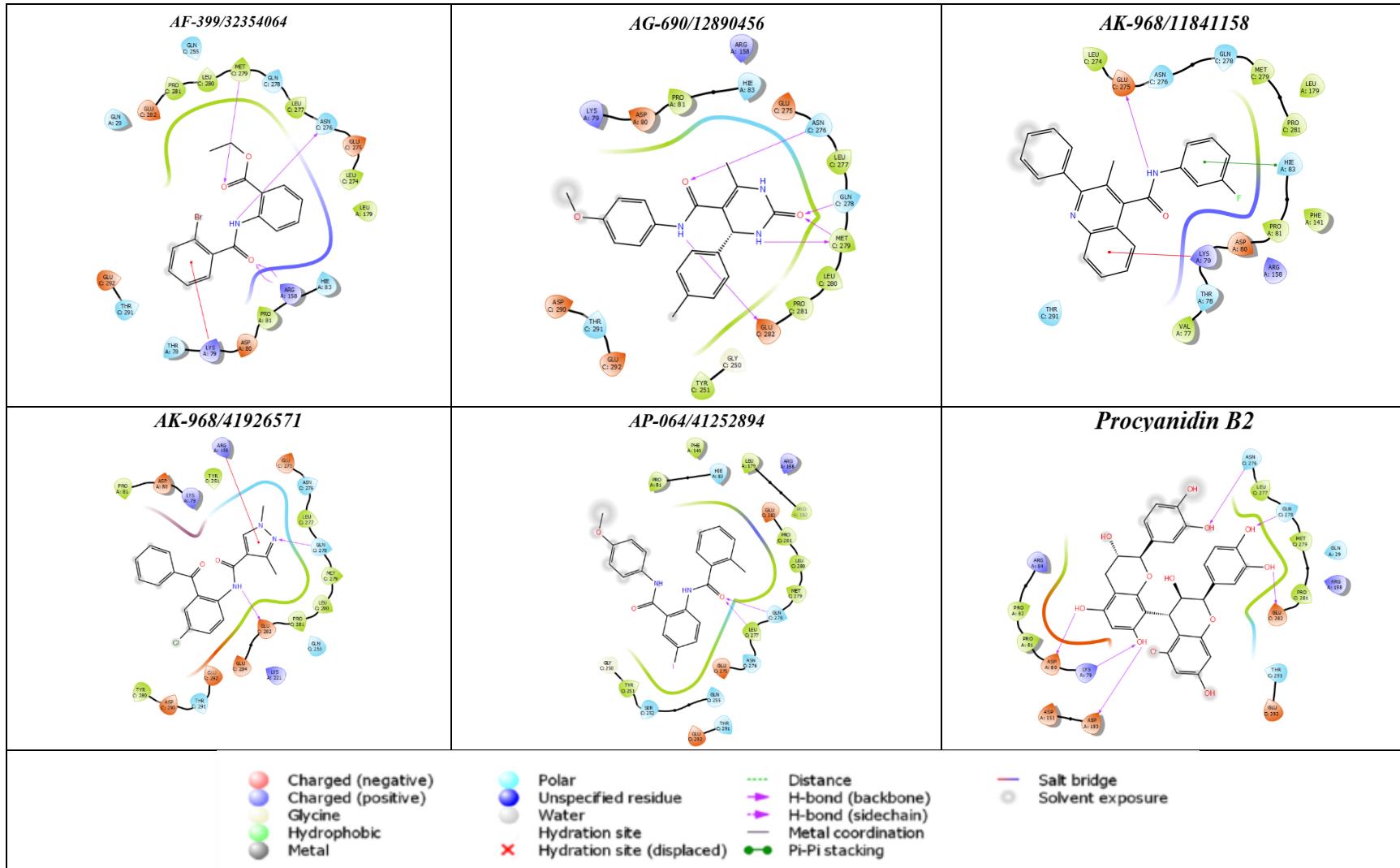


Figure S14. The ligand-protein interaction diagrams of the identified 5 ligands AF-399/32354064, AG-690/12890456, AK-968/11841158, AK-968/41926571 and AP-064/41252894 and the reference compound Procyanidin B2 in the active site of the NF-κB/IκBα complex at the 1 ns pose of the 50 ns MD simulations.

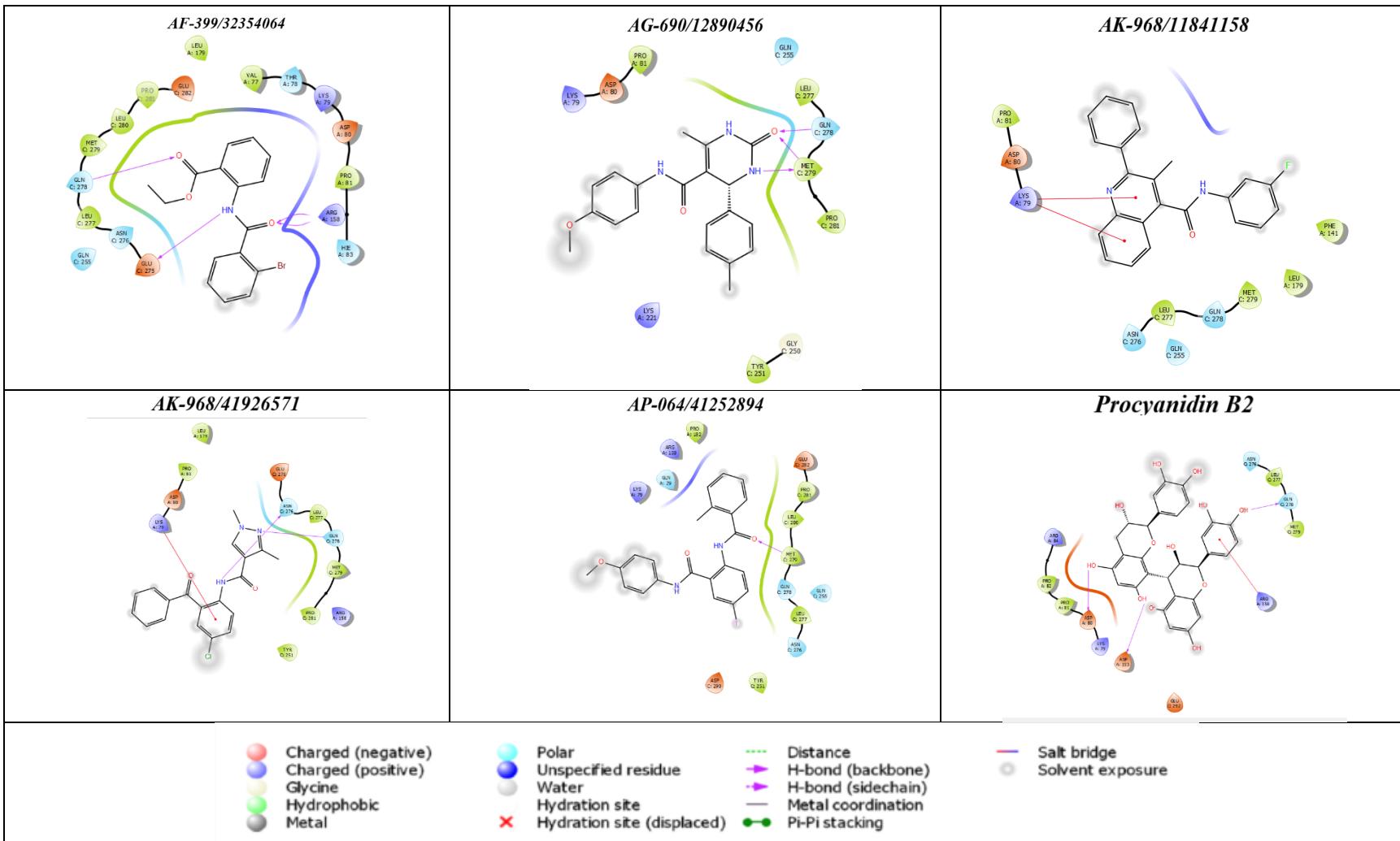


Figure S15. The ligand-protein interaction diagrams of the identified 5 ligands AF-399/32354064, AG-690/12890456, AK-968/11841158, AK-968/41926571 and AP-064/41252894 and the reference compound Procyanidin B2 in the active site of the NF- κ B/IkB α complex at the last (50 ns) pose of the 50 ns MD simulations.

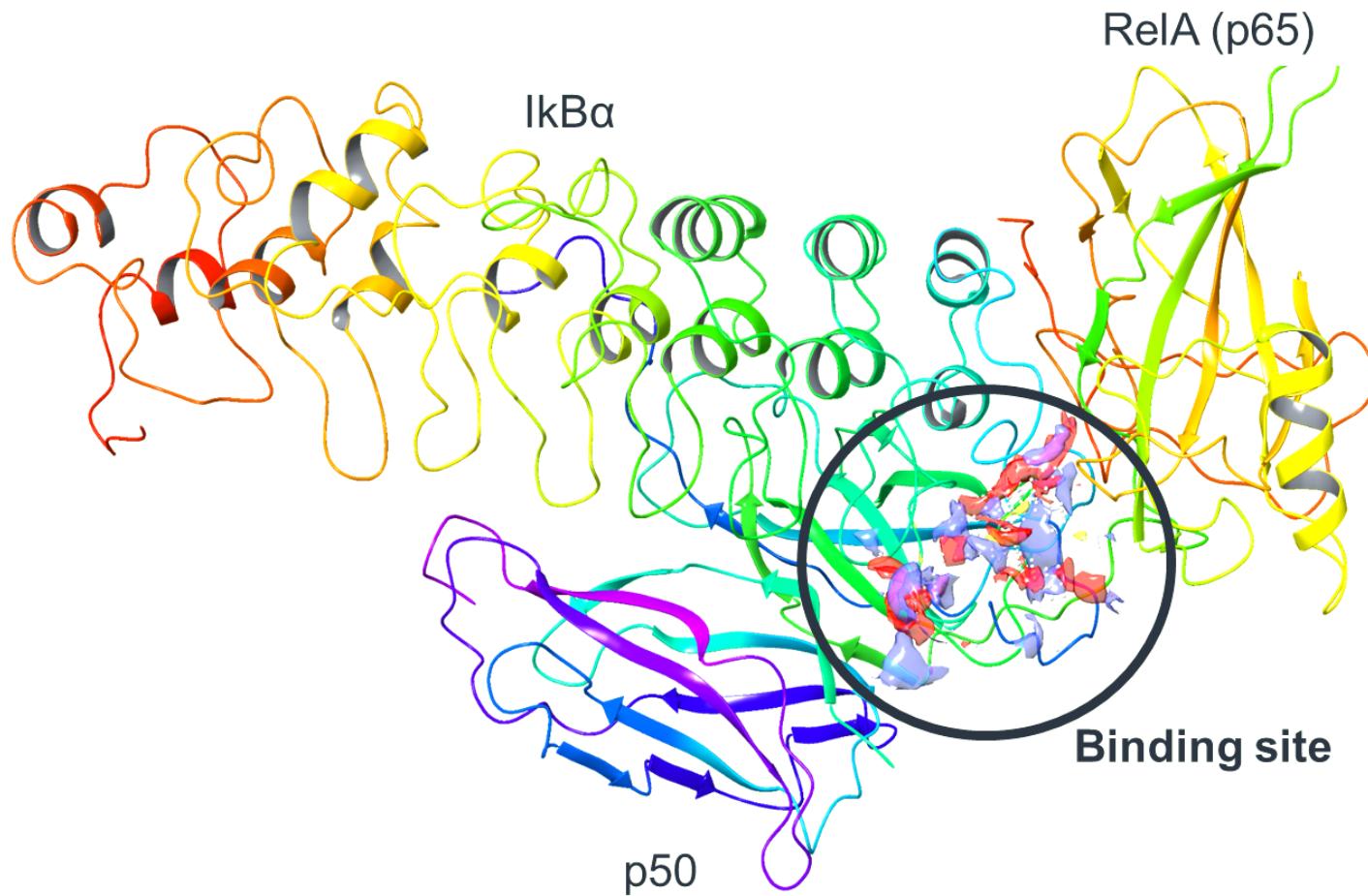


Figure S16. The crystal structure of the NF-κB/IκBα complex with the binding site highlighted by the black circle. This site was used for docking studies and further MD simulations.